

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner,

v.

10X GENOMICS, INC.,
Patent Owner.

Case No. IPR2023-00958
U.S. Patent No. 10,697,013 B1

**PETITIONER'S REHEARING REQUEST
OF THE BOARD'S NON-INSTITUTION DECISION
UNDER 37 C.F.R. § 42.71(d)**

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EX1004	Megan L McCloskey et al., <i>Encoding PCR Products with Batch-Stamps and Barcodes</i> , 45 Biochemical Genetics, 761-767 (2007) (“McCloskey”)
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EX1007	Hubert Hug et al., <i>Measurement of Number of Molecules of a Single mRNA Species in a Complex mRNA Preparation</i> , 221 J. Theor. Bio., 615-624 (2003) (“Hug”)
EX1008	Intentionally left blank.
EX1009	Gerald Schochetman et al., <i>Polymerase Chain Reaction</i> , 158 J. of Infectious Diseases 1154-1157 (1988) (“Schochetman”)
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EX1011	H.C. Yang et al., <i>A genome-wide study of preferential amplification/hybridization in microarray-based pooled DNA experiments</i> , 34 Nucleic Acids Research 1-11 (2006) (“Yang”)
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EX1031	Cole Trapnell, <i>Defining cell types and states with single-cell genomics</i> , 25(10) Genome Research 1491-1498 (2015) (“Trapnell”)
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EX1036	David H. Persing, <i>Polymerase Chain Reaction: Trenches to Benches</i> , J. of Clinical Microbiology 1281-1285 (1991) (“Persing”)
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EX1042	Rami Sukarieh, <i>Relocalization of eIF4E by its binding partners upon stress</i> , Figure 2 (August 2009) at https://www.researchgate.net/publication/41663010_Relocalization_of_eIF4E_by_its_binding_partners_upon_stress
EX1043	Clyde A. Hutchinson, <i>DNA sequencing: bench to bedside and beyond</i> , 35(18) Nucleic Acids Research 6227-6237 (2007) (“Hutchinson”)
EX1044	Beáta G Vértessy and Judit Tóth, <i>Keeping Uracil Out of DNA: Physiological Role, Structure and Catalytic Mechanism of dUTPases</i> , Acc Chem Res. 1-20 (2009) (“Vértessy”)
EX1045	Elaine R. Mardis, <i>Next-Generation DNA Sequencing Methods</i> , 9 Annual Review Genomics and Human Genetics 387-402 (2008) (“Mardis”)
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EX1055	United States Patent Application Publication to McCloskey et al. (“McCloskey II”)
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EX1060	Reinhard Stöger, <i>Epigenetics and Obesity</i> , 9(12) Pharmacogenomics 1851-1860 (2008) at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2652025/ (“Stöger”)

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I. INTRODUCTION

Parse Biosciences, Inc. (“Petitioner”) respectfully requests rehearing of the Board’s decision Denying Institution of *Inter Partes* Review of U.S. Patent No. 10,367,013 (the “’013 patent”). *See* Paper 7 (“Decision”). The Board’s denial is based on a simple misapprehension of both the prior art and the claimed invention.¹

Indeed, the Board’s error in this IPR is irreconcilable with its proper reasoning in *granting* review of U.S. Patent No. 10,155,981 (the “’981 patent”), which addresses claims that are substantially the same as those at issue here. There, the Board recognized the merits of Petitioner’s arguments, and instituted review based on the same prior art relied upon here and in view of virtually identical arguments raised by Patent Owner. *See* IPR2023-00876, Paper 7. Rehearing is warranted here not just to correct the Board’s error, but to rectify the inconsistent results and bring its incorrect decision here in line with its previous decision in IPR2023-00876.

This request is important. Petitioner is an early-stage start-up, and in parallel district court proceeding Patent Owner is seeking to enjoin Petitioner’s sole product line. The PTAB offers the promise of an efficient venue for Petitioner to quickly

¹ The Board’s error here is identical to its error in a related IPR proceeding regarding the related U.S. Patent No. 10,240,197. A request for rehearing on the same basis was filed in that related proceeding. *See* IPR2023-00955, Paper 8.

resolve baseless infringement claims based on invalid patents. It is thus critical that the Board address the Petition carefully based on an accurate understanding of the prior art and proposed grounds.

II. BRIEF SUMMARY OF THE BOARD’S ERROR

The claims of the ’013 patent (like those of the ’981 patent in IPR2023-00876), are directed to a method whereby one modifies nucleic acid molecules, such as DNA or RNA, so that they are “tagged” with two identifiers. A first identifier tracks the particular cell from which each molecule arose, and a second identifier distinguishes one molecule in a cell from other molecules in a cell, including even two molecules that are the *same*. *See* EX1001 at claim 1(b)(ii)-(iii). As recited in dependent claim 23 for instance, the second identifier counts *different* molecules from the same cell that have the *same* sequence. *See id.* claim 23 (“estimating the number of sample polynucleotides having **said sample sequence**”).²

By attaching such identifiers, one can distinguish two otherwise identical DNA molecules in a cell and use that as basis to count how many such molecules were originally present in the cell. *See id.* at claim 1, preamble. Well before the ’013 patent, this had been a typical use of molecular identifiers. *See* EX1002 ¶¶ 71-77, 87-89. Without the distinguishing identifier, typical DNA sequencing methods

² Emphasis supplied unless otherwise stated.

do not yield information sufficient to know whether there was one, or rather multiple, copies of a molecule with a single sequence.

The Board's error is encapsulated in a single paragraph of its decision:

Petitioner's proposal appears to defeat satisfaction of another portion of claim 1, namely a "second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell." Ex. 1001, 30:62–64. For if the second tag is "added to the CDS or TSO after extension," as opposed to the sample polynucleotide, as Petitioner argues (Pet. 39 (emphasis added)), it would appear that the second tag would be incapable of distinguishing any sample polynucleotide from other sample polynucleotides. Rather, *the second tag would be ligated to each and every extension product bearing a CDS or TSO without regard to the sequence of any sample polynucleotide.*

Decision at 16. Thus, the Board concluded that Petitioner's proposed combination of Linnarsson and McCloskey would not include a "tag" that could serve the basic purpose of the claims and allow for one to distinguish among different molecules, but would instead only involve two duplicative tags that served the same purpose of identifying the source (*e.g.*, the cell) from which the molecule originated.

The Board's analysis is based on a factually incorrect assumption that has led to a mistaken outcome. Petitioner did not propose a combination of prior art that would involve the introduction of two *redundant* elements to yield a method that

would not perform an essential claimed function of distinguishing polynucleotides. Patent Owner did not even contend in its preliminary response that this would be the result of Petitioner's combination because there is no support for such a contention.

The Board's error is easy to explain. The Board seemingly believed that both the claimed invention and the McCloskey reference functioned by formulating a one-to-one correspondence between a particular tag and a particular DNA *sequence*, and then adding the particular tag in a *sequence-specific* way so that it pairs-up with its specific partner sequence. Linnarsson, the Board believed, operated in a way incapable of using this mechanism of operation. This, however, misunderstands not just the problem that the claims and McCloskey were seeking to solve, but also the manner in which they solved the actual problem they were seeking to address.

Starting with McCloskey, it was not seeking to introduce tags that could distinguish two *different sequences* by pairing each such sequence with a distinguishable tag in a sequence-specific way. Rather, McCloskey's method introduces tags to distinguish, for instance, two different DNA *molecules* that are present in a sample but that nonetheless have the *same sequence*, i.e., duplicates, such as the two molecules shown below:

ATGGGCAAG ATGGGCAAG

The way McCloskey does this is by adding a *different* tag to each of these molecules in a reaction that is non-specific as to which molecule is which.

In particular, what the Board misunderstood is that, in McCloskey, the tags that are used include a *random* sequence that will differ for any given tag. As such, in the reaction where the tags are added to, for instance, the two molecules above, there is actually a *collection* of tags in the reaction mixture wherein each tag has its own *unique* sequence that is *random*. As McCloskey states, the “barcode is a random sequence,” and the number of “barcodes in a population of oligonucleotides used in a reaction is determined by the number of random bases, n . This enables one to distinguish among 4^n allele *copies* per reaction.” EX1004.004. In other words, one can distinguish up to 4^n sample polynucleotides all with the *same sequence* (*i.e.* “allele *copies*”), by labeling them with 4^n different barcodes.

In McCloskey, when the tags are appended to the molecules, they are appended in a way that is entirely non-specific with regard to the members of the class of sample molecules (*i.e.*, “allele *copies*”) being studied. The ability to later distinguish one copy of a molecule from another (even though they have the same DNA sequence) derives from the fact that copy of the molecule is almost certain to be tagged with a *different* random sequence from the collection of tags precisely *because* the process is non-specific—*i.e.*, one of the many *different* random sequences will *randomly* attach to one molecule. This was a standard approach for distinguishing identical molecules, *i.e.*, copies, which was used not just in McCloskey, but in many other references. See EX1002 ¶ 87.

Turning to the claims themselves, the Board likewise erroneously viewed the claims as requiring one to add tags in a way that can provide a distinction based on a “polynucleotide *sequence*.” Decision at 14. This is wrong, and is a key and critical error. The claims say nothing about distinguishing molecules based on “*sequence*.” Just the opposite, claim 23 requires that molecules being distinguished have the *same sequence*. EX1001 at claim 23 (“estimating the number of sample polynucleotides having said sample sequence”). There thus cannot be a requirement for the tag to distinguish molecules based on a “polynucleotide sequence.”

In sum, as the Petition makes clear, Petitioner’s combination of Linnarsson with McCloskey provided a method for distinguishing polynucleotides, just as the claims require. Patent Owner *never* argued that Petitioner’s proposed combination was based on the introduction of two tags providing duplicative information about the source of a molecule and that could not distinguish identical molecules from the same source. They did not do so because this would be factually erroneous.³

³ In fact, Patent Owner will never present such an argument because the products it accuses of infringing in parallel district court litigation are based on the addition of random tags in a way that is nonspecific with respect to sequence. Were Patent Owner to attempt to distinguish the prior art using a theory along the lines of what the Board relied upon in its institution decision, it would act as an admission by

III. STANDARD OF REVIEW

The Board reviews a non-institution decision for an abuse of discretion. 37 C.F.R. § 42.71(c). “An abuse of discretion occurs when a decision is based on an erroneous interpretation of law or clearly erroneous factfinding, or if that ‘decision represents an unreasonable judgment in weighing relevant factors.’” *In re Gartside*, 203 F.3d 1305, 1315–16 (Fed. Cir. 2000). Misapprehending or overlooking a significant fact or argument is an abuse of discretion. *See Merial Ltd. v. Virbac*, IPR2014-01279, Paper 18 at 7, 8, 14 (P.T.A.B. Apr. 15, 2015).

IV. ARGUMENT

In its Decision, the Board abused its discretion due to erroneous fact finding. The Board found that only one claim limitation was not satisfied: a “second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell.” Decision at 14-16. This element is a part of claim 1, which recites a method of “performing combinatorial tagging to generate a plurality of tagged polynucleotides,” wherein the first step is “providing an extension product by primer extension using a first oligonucleotide tag” capable of

Patent Owner that its claims are non-functional. Notably, in IPR2023-00876 directed to the '981 patent, Patent Owner recently deposed Petitioner's expert. Patent Owner never pursued any questioning along these lines. *See* EX1064.

“distinguishing said sample polynucleotide from sample polynucleotides from other cells” and the second step is “ligating a second oligonucleotide tag” capable of “distinguishing said sample polynucleotide from other sample polynucleotides from said cell.” EX1001 at claim 1.

The Board found that although Petitioner’s proposed combination “appears to satisfy the portion of claim 1 specifying that the second tag must be ligated to an ‘extension product’” it does not satisfy “another portion of claim 1, namely a ‘second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell.’” Decision at 15-16. The Board’s Decision, however, was based on a misunderstanding of how the McCloskey reference operates to provide the claimed “second tag sequence,” as described in detail below.

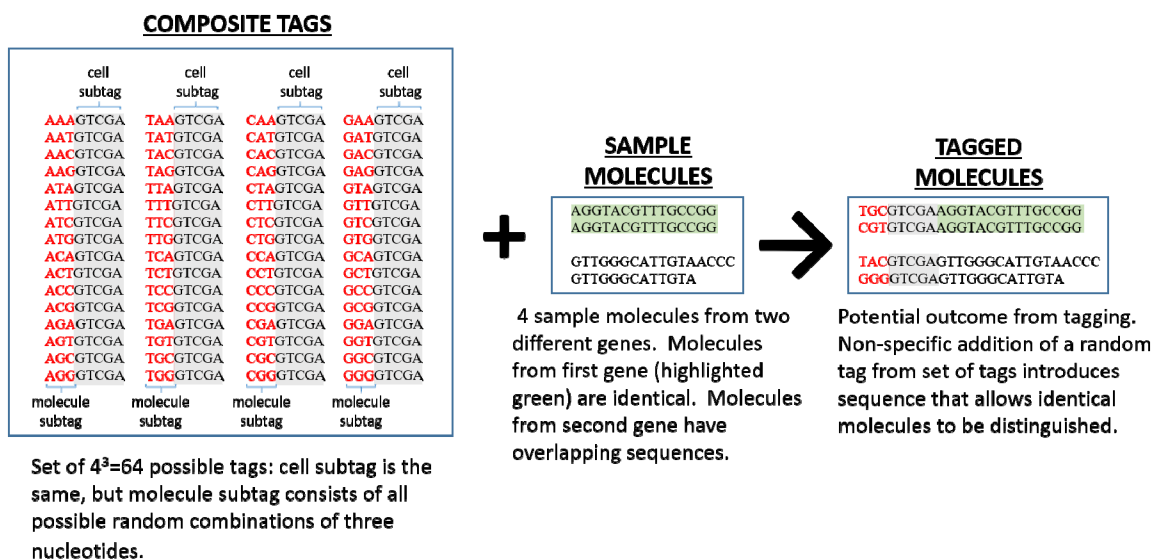
1. Review Of The Key Teachings Of McCloskey

The Board’s error boiled down to a misapprehension of how the prior art McCloskey reference operated. It is thus useful to review McCloskey’s disclosure.

Petitioner proposed a combination based on using McCloskey to modify Linnarsson so as to include a second tag to distinguish between polynucleotides, including duplicates. Pet. at 34-39. Recall that Linnarsson teaches using a single tag to encode which particular cell a polynucleotide originated from. But McCloskey teaches the use of a composite tag with two subtags: one to encode the cell and one to distinguish among identical molecules in a sample.

Specifically, McCloskey teaches an “‘encoding oligonucleotide’ having ‘five distinct information regions,’ *two of which are tag sequences that distinguish, respectively, polynucleotides and samples.*” *Id.* at 22-23. McCloskey’s first subtag sequence, referred to as a “batch-stamp” “is unique to each experiment and is intended to associate a polynucleotide [with] ‘a specific sample’” such as a single cell. *Id.* at 23. McCloskey’s second subtag sequence, however, is a “randomly generated barcode” that allows one to distinguish between redundant sequences (identical sample polynucleotides, i.e., duplicates) because it is *different and unique* to each sample polynucleotide. *Id.* at 22-25. As McCloskey states, the “barcode is a random sequence,” and the number of “barcodes in a population of oligonucleotides used in a reaction is determined by the number of random bases, *n*. This enables one to distinguish among 4^n allele *copies* per reaction.” EX1004.004.

An example of how this works in a simplified scenario is illustrated below:



This example involves 64 composite tags designed to label the molecules in a simplified sample with just four sample molecules originating from a single cell. In this experiment, the first subtag (“cell tag”) is identical in all 64 composite tags (highlighted grey). This identical first subtag sequence (“GTCGA”) functions to identify the cell where the molecule originated. But the second subtag (“molecule tag”) is a random three nucleotide sequence such that *each* of the 64 possible composite tags has a unique and distinguishable second subtag (highlighted red).

These composite tags are then appended to the sample molecules in a reaction where the full set of tags is present (including all 64 random sequences). The particular species of composite tag that becomes appended to any individual molecule is determined entirely at random based purely on which tag happens to react with which molecule. The reaction is not specific for any particular molecule. Nor could it be: the two molecules shown above in green are identical and so the reaction involving those molecules is chemically indistinguishable. Shown above on the right is one of many *potential* outcomes of the reaction. The key point is that because there are many more tags than there are sample molecules, it is unlikely that any two sample molecules will receive the same tag, such that individual molecules, including duplicates, may then be distinguished based on their tag. For instance, the first green molecule has the tag “TGC” and the second one has the tag “CGT.”

To be clear, the McCloskey researchers were studying only a specific

sequence from the *FMRI* locus, and the approach was used to distinguish redundant “allele copies” of molecules from this locus. *Id.* The approach, however, is equally applicable to multiple different loci, and this is what Petitioner proposed by combining McCloskey with Linnarson, a reference where ***all*** mRNA molecules are tagged by primer extension using the polyA tail.

2. The Board Misapprehended The Number Of Unique Second Tags

The Board stated in its Decision that “the second tag would be ligated to each and every extension product bearing a CDS or TSO without regard to the sequence of any sample polynucleotide” Decision at 16. Thus, the Board incorrectly understood Petitioner’s proposed second tag to be a single tag that would be identically appended to all sample polynucleotides from a given source. On this basis, the Board stated that Petitioner’s proposal “would be incapable of distinguishing any sample polynucleotide from other sample polynucleotides.” *Id.*

In fact, as described in the Petition, the second tag in McCloskey is not a singular tag, but rather a “randomly generated barcode” that distinguishes molecules. Pet. at 34-35. In this way, Petitioner’s proposal associates each sample polynucleotide with a ***different and unique*** random sequence exactly as described in McCloskey. *Id.* at 33 (the barcodes “can each include a ***different*** tag”). McCloskey’s “encoding oligonucleotide” includes a “randomly generated barcode” that distinguishes among different “allele copies.” *Id.* at 35. Petitioner’s expert,

explained that the use of a randomly generated oligonucleotide tag was well-known in the art for this purpose. *Id.* at 36-37 (citing EX1002 ¶¶ 71-77, 87-89).

Thus, the Board misapprehended the number of unique second tags utilized in the proposed combination. Petitioner respectfully submits that it described that a multitude of randomly-generated tags (not just one tag) are used to tag the polynucleotides.

3. The Board Misapprehended The Mechanism Of Operation Of McCloskey's Second Tag

In addition to misapprehending the number of second tag sequences in McCloskey, the Board misunderstood how these tags worked in Petitioner's combination. The Board correctly understood that the second tags are “not designed to anneal solely to a *particular* gene or allele.” Decision at 14. While the Board's understanding to this effect is accurate, it misapprehended that this is precisely why the combination would work (not why it would fail).

The claimed method requires a second tag “distinguishing said sample polynucleotide from other sample polynucleotides from said cell.” EX1001, Claim 1. As discussed above and in the Petition, in McCloskey, different molecules (including nucleic acid molecules that have the same sequence) are distinguished from one another by appending a random second tag to a molecule on a random basis. Pet. at 34-35; *supra* Parts 0, IV.1 It does *not* matter which random sequence

is associated with which sample polynucleotide—they are *not* meant to bind specifically. Rather, the fact that each random second tag sequence is different provides a distinction between sample polynucleotides, including duplicates.

The Board’s failure to apprehend this goes to the heart of Petitioner’s motivation to combine Linnarsson with McCloskey, which is to address amplification bias. To illustrate, consider a hypothetical cell with four DNA molecules that all arise from the same gene and have overlapping sequence. Assume that three molecules are actually identical, and that one is different. The “amplification bias” problem is that when one amplifies these molecules (*e.g.*, by PCR) for subsequent analysis by sequencing, the single different molecule may well be preferentially amplified over the three identical molecules. If one then attempts to use the DNA sequencing data to count how many copies of each molecule were originally present by counting the number of sequence reads with a particular sequence, the results will be distorted because of the amplification bias.

The molecule subtag in McCloskey overcomes this. By tagging each of the four starting polynucleotide molecules uniquely—regardless of their sequence—one can amplify the four molecules and sequence them and then later use the tag to discern the original molecule from which each sequence read arose. *See* Pet. at 35-37. By counting unique tags, one can determine how many individual DNA molecules were present in the original sample and even distinguish different DNA

molecules that are nonetheless identical in sequence. As McCloskey states, “counting sequences with *nonredundant barcodes* provides a quantitative measure of template diversity.” EX1004.006. Petitioner’s expert explained that this very approach had been used not just in McCloskey, but in several other prior art references. *See* EX1002 ¶ 89.

4. The Board’s Decision Not To Institute Here Is Irreconcilable With Its Decision To Institute In IPR2023-00876

Claim 1 of the ’013 patent requires merely that the “second tag sequence *distinguish[] said sample polynucleotide from other sample polynucleotides from said cell.*” EX1001 at Claim 1. Thus, all that is required for the satisfaction of this limitation is that the tag is unique to the molecule. McCloskey teaches precisely such a tag. As Petitioner explained, McCloskey teaches a “barcode” to distinguish different “allele copies” from a sample. Pet. at 34-35.

Critically, the Board already acknowledged that this disclosure satisfies the function of the second tag in instituting review of the ’981 patent, which includes claims little different from those at issue here. *See* IPR2023-00876, Paper 7. In that case, the Board adopted the rationale of Petitioner’s declarant—which is the same rationale presented here—that Linnarsson’s tag sequence could be easily modified to perform “the function of McCloskey’s ‘barcode’, used to differentiate polynucleotides within a cell.” *Id.* at 22. The Board understood the second tag of

the prior art to be a sequence capable of differentiating polynucleotides:

Petitioner proposes, with declaration testimony in support, that “Linnarsson’s tagged oligonucleotides—CDS or TSO—could be modified through routine methods to incorporate a second tag to uniquely identify each sample polynucleotide.” In particular, Petitioner’s declarant, Dr. Cooper, testifies that a person of ordinary skill “could conceptually divide each of Linnarsson’s cell-tag sequence into two portions, wherein the first portion performs the function of McCloskey’s ‘batch-stamp,’ used to track individual cells, *and the second portion performs the function of McCloskey’s ‘barcode’, used to differentiate polynucleotides within a cell.*”

We are persuaded there is a reasonable likelihood that Petitioner will prevail in demonstrating an adequate reason for a person of ordinary skill in the art to have combined Linnarsson and McCloskey.

Id. at 21-22. The Board correctly concluded that this established a reasonable likelihood that a skilled artisan would have combined the references to satisfy the claim. *Id.* at 22.

Petitioner’s proposed combination and rationale that it presented with respect to the ’981 Patent are the same as what it represents with respect to the ’013 Patent. The Board’s denial here—based on the rationale the Petitioner is proposing a non-functional combination of art—is thus irreconcilable with its previous decision and turns on an erroneous new interpretation of the record. This inconsistency is yet further reason for the Board to reconsider its decision in this case.

V. CONCLUSION

The Board should institute review.

Dated: January 5, 2024

Respectfully submitted,

/Derek C. Walter/

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CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing **PETITIONER'S REHEARING REQUEST OF THE BOARD'S NON-INSTITUTION DECISION UNDER 37 C.F.R. § 42.71(d)** are being served on January 5, 2024, via electronic mail pursuant to 37 C.F.R. § 42.107 to the Patent Owner at the address below:

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